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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/075,542	02/15/2002	Guiyi Zhang-Sun	104385-145	8618

7590 10/14/2003

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,542	ZHANG-SUN ET AL.	
	Examin r	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims examined on the merits are 1-26 which are all claims in the application.

Specification

The disclosure is objected to because of the following informalities: in the specification at page 3, line 2, following "Summary of the Invention", the meaning of "polylyside" is uncertain. Is this a misspelling?

Appropriate correction or clarification is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for forming a matrix stabilized enzyme crystal when using a polymer as required by claim 11 and a multifunctional crosslinking reagent that is a dialdehyde as required by claim 6, and using an amount of crosslinking reagent as required by claim 8, does not reasonably provide enablement for using other polymers and crosslinking reagents, and amounts of crosslinking reagent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not enable using any polymer and crosslinking reagent. It would be unpredictable as to results when using a polymer and crosslinking reagent substantially different from those disclosed in the specification. The specification discloses that the amount of crosslinking reagent must be low, and clearly higher amounts will not work.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-26 are confusing and unclear by reciting "matrix stabilized enzyme crystals" since it is uncertain as to what constitutes the matrix and the physical and chemical relationship between the matrix and the enzyme crystals, and the polymer and the cross-linking reagent when required.

Claims 1-20 are further confusing and unclear by claim 1 failing to set forth clear, distinct and positive process steps. It is unclear when in the method the polymer and crosslinking reagent are

added to the enzyme crystals, and whether the cross-linking reagent reacts with the polymer or enzyme crystals or both.

In claim 21, "PAL" is uncertain as to the material required. The abbreviation should be replaced by the full name.

Claims 23 and 26 are confusing and unclear as to the invention claimed by not requiring both a polymer and cross-linking reagent since the specification fails to describe performing the invention to produce a matrix in the absence of the cross-linking reagent and polymer.

Claim 24 is confusing and unclear by reciting "cross-linking polylysine with phenylalanine ammonia lyase" since it is unclear from the specification how an enzyme can be used to cross-link a polymer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of

each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-8, 11-14, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolin et al (6,541,606 B2) in view of Mucke (4,940,664).

The claims are drawn to a method of forming matrix stabilized enzyme crystals by cross-linking enzyme crystals with a polymer using a multi-functional cross-linking reagent. Also claimed are resultant matrix stabilized enzyme crystals.

Margolin et al discloses stabilizing protein crystals by encapsulating the protein crystals in a polymer (paragraph bridging cols 12 and 13, and paragraph bridging cols 28 and 29) such as poly (amino acids) (col 28, line 52), poly (esters) (col 28, line 53) or polyols (col 28, line 59). The protein crystals may be crosslinked (col 24, line 28 to col 27, line 29) with a multifunctional crosslinking agent containing aldehyde reactive groups (col 25, lines 32-39) such as glutaraldehyde (col 51, line 53). The protein crystal may be an enzyme crystal (col 13, line 20) such as a lyase or lipase (col 16, lines 64 and 66), and the enzyme crystal may crosslinked (col 51, line 50). The amount of crosslinking agent may be 1.5% (col 52, line 46). Rate of dissolution of the polymer encapsulated protein crystals may be modulated by varying polymer crosslinking (col 5, line 47).

Mucke discloses stabilization of carrier-bound enzymes by treatment with a bifunctional crosslinking agent such as glutaraldehyde (col 3, line 22) and a polyamine such as polyethylene imine (col 3, line 30). An enzyme may be bound to an inorganic carrier and the enzyme on the carrier then crosslinked with glutaraldehyde (col 4, lines 30-61) to produce the carrier bound enzyme which is then treated with glutaraldehyde and polyethylene imine (col 4, lines 64-68).

When producing a polymer encapsulated enzyme crystal as disclosed by Margolin et al, it would have been obvious to use a polyamino acid as the polymer as taught by Margolin et al, and it would have been further obvious to use a glutaraldehyde to crosslink the polyamino acid as suggested by Mucke using glutaraldehyde to crosslink a polyamine on a carrier bound enzyme and by Margolin et al disclosing that rate of dissolution can be modulated by varying polymer crosslinking (col 5, line 47). A polyamino acid polymer disclosed by Margolin et al would have been expected to contain amino groups reactive with aldehyde groups of glutaraldehyde in the same type of way that aldehyde groups of glutaraldehyde react with amino groups of a polyamine when carrying out the process of Mucke. Using polylysine as a polyamino acid as in claim 14 would have been an obvious matter of choice within the skill of the art. As noted above, Margolin et al disclose using 1.5% crosslinking agent to crosslink enzyme crystals. It would have been obvious to use this amount of crosslinking agent in

combination with the polyamino acid polymer, and this amount is less than 2% as required by claim 8.

Claim Rejections - 35 USC § 103

Claims 9, 10, 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 1, 2, 4-8, 11-14, 18 and 19 above, and further in view of Margolin et al (6,140,475).

The claims require amounts of crosslinking reagent of 0.5% or less and 0.2% or less.

Margolin et al ('475) disclose crosslinking enzyme crystals to obtain crosslinked enzyme crystals having controlled dissolution by using an amount of glutaraldehyde in a range of about 0.1 to about 0.2% (col 48, line 29).

When modifying Margolin et al ('606) as set forth above by encapsulating enzyme crystals in a polyamino acid polymer crosslinked with glutaraldehyde, it would have been obvious to use an amount of glutaraldehyde as taught by Margolin et al ('475) for obtaining controlled dissolution since Margolin et al ('606) teach that dissolution rate can be modulated by varying polymer crosslinking (col 5, lines 44-47).

Claim Rejections - 35 USC § 103

Claims 3, 15, 20-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims, 2, 4-8, 11-14, 18 and 19 above, and further in view of Eigtved et al (5,753,487).

The claims require the enzyme to be phenylalanine ammonia lyase, and claim 23 requires a method of treating hyperphenylalaninemia with the matrix stabilized enzyme crystals.

Eigtved et al disclose stabilizing phenylalanine ammonia lyase by crosslinking with glutaraldehyde (col 10, lines 25-26), and using the crosslinked phenylalanine ammonia lyase to treat hyperphenylalaninemia (col 12, lines 23-36).

When modifying Margolin et al ('606) as set forth above, it would have been obvious to use phenylalanine ammonia lyase as the enzyme encapsulated to obtain the function of the phenylalanine ammonia lyase to treat hyperphenylalaninemia as suggested by Eigtved et al.

Claim Rejections - 35 USC § 103

Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 3, 15, 20-23 and 26 above, and further in view of Margolin et al ('475).

The claims require an amount of crosslinking agent of less than 0.5% and using polylysine as the polymer when treating hyperphenylalaninemia with phenylalanine ammonia lyase as required by claim 23.

Margolin et al ('475) is described above.

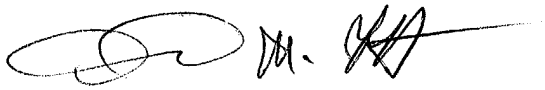
For reasons set forth above when applying Margolin et al ('475), it would have been obvious to use an amount of glutaraldehyde for crosslinking as taught by Margolin et al ('475) for controlled dissolution as the amount of crosslinking agent used to modulate rate

of dissolution by varying polymer crosslinking as taught by Margolin et al ('606).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 703-308-0520. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 703-308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



David M. Naff
Primary Examiner
Art Unit 1651

DMN
10/9/03